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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO.
09/787,443	07/30/2001	Lars Christian Ronn	P66506US0	6998

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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	13

DATE MAILED: 04/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,443	RONN ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-97* is/are pending in the application.

4a) Of the above claim(s) *67-69 and 74-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-66 and 70-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 July 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10,11*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election **with** traverse of Group I (claims 56-66 and 70-73) drawn to SEQ ID NO: 1 in Paper No. 9 (14 March 2003) is acknowledged. The traversal is on the ground(s) that the lack of unity as set forth in Paper No. 7 (14 January 2003) failed to apply the standards for determining unity of invention in accordance with PCT Rule 13. This is not found persuasive because Group I as set for in Paper No. 7 (14 January 2003) is drawn to SEQ ID NO: 1, a special technical feature which is not required by ALL 18 groups. The decision by the Swedish Patent and Registration Office (PRV) regarding unity of invention has been taken into consideration by the Examiner and while interesting, the laws governing patents in the Kingdom of Sweden do not apply to the United States of America and therefore is not found persuasive. The requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments, and/or Claims

2. The Preliminary Amendment received 29 March 2001 (Paper No. 1 1/2) has been entered in full. Claims 1-55 have been cancelled and claims 56-97 have been added.

3. Claims 67-69 and 74-97 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

4. Claims 56-66 and 70-73 are under examination as they pertain to SEQ ID NO: 1.

Drawings

5. The drawings are objected to because each of Figures 3, 19, and 22 have two separate images which must be labeled "i.e. 3A and 3B, 19A and 19B, 22A and 22B". A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Sequence Rules

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below. This application discloses an amino acid sequence on Figures 4, 7, 17, and 20 without a corresponding SEQ ID NO. Correction is required. If the SEQ ID NO's disclosed in Figures 4, 7, 17, and 20 have been already submitted and only the notation omitted, this may be obviated by amending the Figure to include the SEQ ID NO.

7. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. This application discloses an amino acid sequence on pp. **58 lines 25-29**. Correction is required.

Oath/Declaration

8. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because: Inventor Peter Jensen did not date the Oath/Declaration under his signature.

Specification

9. The disclosure is objected to because of the following informalities: underlining and other non-initialed marks on the specification (pp. 23 lines 16-17 and 29-33; pp. 24 lines 8-13 and lines 30-35; pp. 33 lines 30-31; pp. 45 lines 7-19 and 23; pp. 47 lines 16 and 26; pp. 61 lines 13, 15, 19, 20). Appropriate correction is required.

Claim Objections

10. Claims 56, 60, and 61 are objected to because of the following informalities: the claims recite non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims **56-66** and **70-73** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO: 1, does not reasonably provide enablement for an amino acid sequence having at the most 12 amino acid residues from the amino acid sequence of neural cell adhesion molecular (NCAM) or a mimic thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

12. The claims are drawn to a compound comprising an amino acid sequence having at the most 12 amino acid residues from the amino acid sequence of neural cell adhesion molecular (NCAM) or a mimic thereof. The language of said claims encompasses non-elected subject matter, fragments, derivatives, and analogs of SEQ ID NO: 1.

13. The specification teaches that SEQ ID NO: 1, or "C3" as it is referred to in the instant specification, has the following properties: (a) an amino acid sequence of A-S-K-K-P-K-R-N-I-K-A (SEQ ID NO: 1), (b) exhibits a dose dependent response in stimulating or promoting neurite outgrowth (Figure 10), (c) inhibits aggregation formation of primary hippocampal neurons, (d) stimulates or promotes proliferation of primary hippocampal neurons, (e) is capable of biding to the NCAM Ig1 domain.

14. In order to practice the invention the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations with known peptides and analogs to correlate with SEQ ID NO: 1's activity. As shown in Figure 7 of the instant application some peptides have no apparent action ("117, 118, 119") while others show strong activity (i.e. C3 or SEQ ID NO: 1). In the absence of any guidance from the specification,

the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

15. For instance, in the instant application in Figure 7 peptide "117" contains a two single amino acid changes from K to A at position 6 and R to A at position 7 which obliterates the tested activity. And in Figures 19 and 21, single amino acid changes have significant effects on the Ig2-peptide. Finally, in Figure 25, it is clear that mutations in NCAM can greater reduce its functionality.

16. Furthermore, the specification fails to provide any guidance for the successful use of mimics and as the specification shows that different peptides have different effects (Figures 7-11), the activity of any given peptide is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. As noted by the Applicant:

> "The substitution of only two basic amino acids in the sequence of the C3 (SEQ ID NO: 1) peptide completely abolished the neuritogenic effect." (pp. 41 lines 34-35).

17. Thus specification as filed does not provide any guidance or examples that would enable a skilled artisan to make the claimed peptides and mimics of SEQ ID NO: 1. Additionally, a person skilled in the art would recognize that predicting the efficacy of making variants with the same activity as SEQ ID NO: 1 based solely on the performance of a single isoform is highly problematic. Thus, although the specification prophetically considers and discloses general properties of the claimed peptides and mimics, such a disclosure would not be considered enabling since the activity of any given peptide is highly unpredictable. It is not plausible to extrapolate the concentrations and their effects for variants and mimics of SEQ ID NO: 1.

18. The factors listed below have been considered in the analysis of enablement:

a. The breadth of the claims;
b. The nature of the invention;
c. The state of the prior art;
d. The level of one of ordinary skill;
e. The level of predictability in the art;
f. The amount of direction provided by the inventor;
g. The existence of working examples; and
h. The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

19. The following references are cited herein to illustrate the state of the art of neural cell adhesion molecules.

20. Due to the broad claim language, the claims are drawn to all fragments and mimics of neural Cell Adhesion Molecule (NCAM) so long as they comprise approximately 12 amino acids. Frei et al. (July 1992) "Different Extracellular Domains of the Neural Cell Adhesion Molecule)N-CAM) Are Involved in Different Functions." The Journal of Cell Biology 118(1): 177-192 (**IDS #BC**) teaches that fragments of NCAM differ in their effectiveness is stimulating neurite outgrowth (Table I). Thus a skilled artisan is presented with a burden of experimentation to determine which mimics of SEQ ID NO: 1 are useful for making the invention.

21. The state of the art according to Doherty et al. (March 1995) "The Neural Cell Adhesion Molecule and Synaptic Plasticity." J. Neurobiol. 26(3): 437-446 teaches that NCAM isoforms differ in their ability to stimulate neurite outgrowth (Table 1). Further, neurons differ in their ability to sense and respond to different NCAM levels and isoforms (pp. 440). Thus the prior art teaches a degree of variation in NCAM isoform (a category of mimics) and neuronal response to them.

22. Concerning the predictability of the NCAM art, Rao et al. (August 1992) "Identification of a Peptide Sequence Involved in Homophilic Binding in the Neural Cell Adhesion Molecule (NCAM)" The Journal of Cell Biology 118(4): 937-949 (**IDS #DE**) who teaches several peptide analogues of NCAM with and without activity cell aggregation inhibition activity (Table III, IV, and V). This point is further illustrated by Rao et al. (4 November 1994) "Mechanism of Homophilic Binding Mediated by the Neural Cell Adhesion Molecule NCAM." The Journal of Biological Chemistry 269(44): 27540-27548 (**IDS #DF**) who teaches that peptides which mimic NCAM activity vary in their sensitivity to mutation. For instance, in the peptide defined as Lys-243 to Glu-252, the substitution of a single amino acid such as Tyr-244 or Phe-246 with Ala lead to a substantial reduction in NCAM homophilic binding activity whereas substitution of Ser-245 and Asn-247 with Ala do not effect activity (Figures 9- 11). Thus a skilled artisan, to make the invention to its full scope, would be unable to predict the activity of any given NCAM peptide or mimic but would have to resort to trial and error to determine which peptides and/or mimics have the desired activity.

23. Therefore it is evident that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also

be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1): 34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427). Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to

same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

24. Regarding amino acid sequences having at most 12 amino acid residues from the amino acid sequence of neural cell adhesion molecule (NCAM) and mimics thereof, the art recognizes that the aforementioned peptides and analogs can pertain to almost any given agent as long as it comprises 12 amino acids from NCAM. Due to the large quantity of experimentation necessary to identify all the applicable peptides and mimics, the lack of direction/guidance presented in the specification regarding synthesizing, screening, and evaluating all applicable peptides and mimics, the absence of working examples directed to known peptides and mimics, the complex nature of the invention, the unpredictability of the effects of peptides and mimics on cells and/or patients (**see references above**) and the breadth of the claims which fail to recite limitations for what constitutes an applicable peptides and mimics, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

25. Claims **56** and **60** rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

26. The term "at the most" in claim 56 is a relative term which renders the claim indefinite. The term "at the most" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably

apprised of the scope of the invention. This phrase can be construed to mean any peptide from a single amino acid to 12 amino acids, thus covering a broad and ill-defined range of peptides. The metes and bounds of said phrase are not clear from the specification or claim 56.

27. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 60 recites the broad recitation "*more suitably*", and the claim also recites "*even more suitably*" and then "*most suitably*" which are narrower statements of the first limitation.

Summary

28. Claims 56-66 and 70-73 are hereby rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
April 11, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER